

Supplementary material

Supplementary table 1. Longitudinal sub-model summary of neuropsychological performance over time.

Outcome	Predictor	β	95% CI	p	Outcome	Predictor	β	95% CI	p
ECAS total	Time (spline 1)	0.45	-0.04 – 0.94	.07	ECAS ALS Specific	Time (spline 1)	0.12	-0.58 – 0.80	.69
	Time (spline 2)	0.30	-0.24 – 0.81	.27		Time (spline 2)	0.05	-1.06 – 1.11	.89
	Age	-0.03	-0.04 – -0.02	<.001		Age	-0.03	-0.03 – -0.01	<.001
	Cognitive reserve	0.37	0.11 – 0.64	.003		Cognitive reserve	0.40	0.21 – 0.59	<.001
	CR x time (spline 1)	-0.03	-0.73 – 0.68	0.92		CR x time (spline 1)	-0.15	-1.08 – -0.81	.74
	CR x time (spline 2)	0.04	-0.75 – 0.82	0.94		CR x time (spline 2)	-0.17	-1.65 – 1.35	.81
ECAS ALS Non-Specific	Time (spline 1)	0.34	-0.19 – 0.90	.21	RMET	Time (spline 1)	0.25	-0.49 – 0.96	.51
Time (spline 2)	-1.98	-2.07 – -1.86	<.001	Time (spline 2)		-0.07	-0.35 – 0.23	.62	
Age	-0.02	-0.03 – -0.01	<.001	Age		-0.05	-0.07 – -0.03	<.001	
Cognitive reserve	0.26	0.06 – 0.45	.01	Cognitive reserve		0.66	0.26 – 1.04	.002	
CR x time (spline 1)	0.73	-0.05 – 1.51	.07	CR x time (spline 1)		-0.25	-1.33 – 0.81	.63	
CR x time (spline 2)	2.15	1.99 – 2.33	<.001	CR x time (spline 2)		-0.15	-0.59 – 0.28	.43	
Verbal Fluency (Unrestricted)	Time (spline 1)	-0.20	-1.55 – 1.13	.77	Verbal Fluency (Restricted)	Time (spline 1)	0.95	0.04 – 1.80	.05
	Time (spline 2)	0.07	-0.52 – 0.66	.82		Time (spline 2)	-0.05	-0.76 – 0.61	.89
	Age	-0.03	-0.05 – -0.01	.005		Age	-0.02	-0.05 – 0.01	.32
	Cognitive reserve	0.49	-0.15 – 1.16	.13		Cognitive reserve	0.61	-0.73 – 1.99	.39
	CR x time (spline 1)	-0.27	-2.22 – 1.69	.78		CR x time (spline 1)	-0.89	-2.19 – 0.34	.17
	CR x time (spline 2)	-0.26	-1.08 – 0.58	.54		CR x time (spline 2)	0.07	-0.94 – 1.10	.89
CWIT Inhibition	Time (spline 1)	-0.48	-0.87 – -0.07	.03	BNT	Time (spline 1)	-0.25	-0.95 – 0.45	.48
	Time (spline 2)	0.44	-0.20 – 1.12	.16		Time (spline 2)	-0.26	-1.08 – 0.53	.51
	Age	-0.08	-0.11 – -0.05	<.001		Age	-0.03	-0.05 – -0.01	.001
	Cognitive reserve	0.87	0.27 – 1.49	.01		Cognitive reserve	0.55	0.13 – 0.98	.01
	CR x time (spline 1)	0.14	-0.40 – 0.65	.58		CR x time (spline 1)	0.26	-0.75 – 1.26	.64
	CR x time (spline 2)	-0.92	-1.82 – -0.05	.04		CR x time (spline 2)	0.20	-0.98 – 1.34	.72
CWIT Switching *	Time	-1.04	4.00 – 1.93	.50	RAVLT total *	Time	-1.49	-9.86 – 6.63	.72
	Age	-0.06	-0.09 – -0.04	<.001		Age	-0.04	-0.06 – -0.02	<.001
	Cognitive reserve	0.63	0.17 – 1.07	.008		Cognitive reserve	0.29	-0.02 – 0.59	.07
	CR x time	0.56	-3.12 – 4.26	.78		CR x time	-4.49	-14.99 – 6.55	.41

RAVLT	Time (spline 1)	0.11	-0.23 – 0.44	.50	LM	Time (spline 1)	0.05	-0.34 – 0.49	.84
delayed	Time (spline 2)	-0.08	-1.22 – 1.05	.91	Immediate	Time (spline 2)	-0.57	-0.96 – -0.14	.009
	Age	-0.04	-0.06 – -0.02	<.001		Age	-0.04	-0.06 – -0.02	.002
	Cognitive reserve	0.21	-0.15 – 0.58	.25		Cognitive reserve	0.38	0.03 – 0.72	.04
	CR x time (spline 1)	-0.27	-0.72 – 0.17	.22		CR x time (spline 1)	-0.73	-1.32 – -0.17	.02
	CR x time (spline 2)	-0.52	-1.84 – 1.01	.57		CR x time (spline 2)	0.20	-0.30 – 0.72	.44
LM Delayed	Time (spline 1)	0.11	-0.23 – 0.44	.50					
	Time (spline 2)	-0.08	-1.22 – 1.05	.91					
	Age	-0.04	-0.06 – -0.02	<.001					
	Cognitive reserve	0.21	-0.15 – 0.58	.25					
	CR x time (spline 1)	-0.27	-0.72 – 0.17	.22					
	CR x time (spline 2)	-0.52	-1.84 – 1.01	.57					

* Splines not added as they did not improve the fit of the model

Model Specification

Joint longitudinal and time-to-event models are composed of two sub-models, a Cox survival model and a longitudinal mixed effects model. The dependence between the two sub-models is captured through the association structure. In this case a current value association structure was chosen, which assumes the log hazard function of the event at time t is linearly associated with the longitudinal sub-model predictor at time t .

Cox survival model

Known risk factors for shorter survival in ALS were included in the Cox model, i.e. age, diagnostic delay, site of onset and C9orf72 positive status. The Cox survival model is:

$$h_i(t) = h^0(t) \times \exp(\alpha^1 \times m_i(t) + b^1 x_i^1 + b^2 x_i^2 + b^3 x_i^3 + b^4 x_i^4)$$

or

$$h_i(t) = h^0(t) \times \exp(\alpha^1 * m_i(t) + b^1(\text{age}_i) + b^2(\text{diagnostic delay}_i) + b^3(\text{site of onset}_i) + b^4(\text{C9orf72}_i))$$

where: (t) is survival time, h(t) is the hazard function determined by covariates x^1, x^2, x^3, x^4 . h^0 is the baseline hazard where x^1, x^2, x^3 and x^4 equal 0. α^1 is the association parameter, representing the strength of association between the longitudinal outcome measure (i.e. cognitive score) and the time-to-event outcome. $m_i(t)$ is the expectant value predicted by the longitudinal model for a given individual at time = t.

$x^1 = \text{age}$, $x^2 = \text{diagnostic delay}$, $x^3 = \text{site of onset}$, $x^4 = \text{C9orf72 status}$. The coefficients b^1, b^2, b^3, b^4 measure the effect size of each covariate.

Longitudinal Mixed Effects Model

Longitudinal mixed effects models were fit for each outcome measure. Time was defined by months since baseline assessment. Natural cubic splines with two degrees of freedom were added to cater for non-linear trends over time. Age, CR and a time by CR interaction were included as fixed effects. Random intercepts and random slopes for time were included. The mixed effects equation for each outcome measure is:

$$m_i(t) = \beta^0 + \beta^1 x^1_i + \beta^2 x^2_i + \beta^3 x^3_i + \beta^4 x^4_i$$

or

$$m_i(t) = \beta^0 + \beta^1(\text{time}_i) + \beta^2(\text{age}_i) + \beta^3(\text{CR}_i) + \beta^4(\text{CR} * \text{time}_i) + \varepsilon_i$$

where

$$y_i(t_{i,j}) = m_i(t_{i,j}) + \varepsilon_{i,j}$$

and $y_i(t_{i,j})$ represents the j th observational value for patient i at time $t_{i,j}$

and $x^1 = \text{time}$, $x^2 = \text{age}$, $x^3 = \text{CR}$, $x^4 = \text{CR by time interaction}$, $\varepsilon = \text{random error}$. Models were evaluated comparing Akaike's information criterion (AIC), Bayesian information criterion (BIC) and log likelihood ratio test.